REMARKS

This is being filed in Response to the Office Action dated May 6, 2004. Applicants herein amend Claims 1 and 11 and request cancellation of Claims 2 and 17. Thus, upon entry of the amendment, the pending claims are Claims 1, 3-9, 11-16, and 18-21.

Applicants note, with appreciation, that the Examiner has withdrawn the rejection of claim 16 under 35 U.S.C. 112, second paragraph in view of the Applicants' amendment.

Applicants also note, with appreciation, the withdrawal of rejections under 35 U.S.C. 102(e) over U.S. Patent No. 6,506,594 ("Barany"), 6,495,319 ("Harney"), U.S. Patent No. 6,489,466 ("Huang"), U.S. Patent No. 6,479,262 ("Delagrave").

Applicants also note, with appreciation, the withdrawal of the rejection of claims 1 and 11-21 under 35 U.S.C. 103(a) over Delagrave and Barany.

Claim 1 has been amended herein to incorporate the subject matter of claim 2, and accordingly, Applicants request cancellation of claim 2 without prejudice. Likewise, Claim 11 has been amended herein to incorporate the subject matter of claim 17, and accordingly, Applicants request cancellation of claim 17 without prejudice. The claim dependency for Claims 18 and 19 have been changed from canceled Claim 17 to base Claim 11.

Both claims 1 and 11 have been amended to include the feature that the ligation may be performed using a ribozyme. This feature is supported in the specification at page 13, line 21. Thus, no new matter is added.

Maintained Rejections

Double Patenting

Claims 1-5, 7, 8, 11-15, 17, and 18 are rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1, 7, 10, 12, 14, 18, 20, 21, and 24-26 of U.S. Patent No. 6,479,262 to Delagrave ("Delagrave I").

The Office Action argues that the inclusion of coupled nucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide was within the purview of the skilled artisan. Applicants respectfully disagree. Delagrave I discloses the assembly of oligonucleotide chains in which subunits of the chain are ligated in succession and subsequently amplified by PCR. In contrast, Applicants include the feature of coupled

nucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide. That feature is recognized as important when one knows that the coupled nucleotides may then be mixed and used in a PCR reaction such that longer oligonucleotides may be formed enzymatically with a variety of predictable sequences. It is the Applicants disclosure which teaches this and not the claims of Delagrave I. Applicants caution against hindsight reconstruction.

Further, if the Examiner believes that the inclusion of the feature of coupled nucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide is merely a design choice well known in the art, Applicants request a reference supporting that assertion or an affidavit under 37 CFR 1.104(d)(2) if such is within the personal knowledge of the Examiner.

New Rejections

Rejections Under 35 U.S.C. 103(a)

A. U.S. Patent No. 5,942,609 to Hunkapiller *et al.*

Claims 1-2, 4-9, 11-15, 17 and 19-21 are rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,942,609 to Hunkapiller *et al.* ("Hunkapiller").

Hunkapiller describes a method of polynucleotide synthesis requiring immobilizing a first assembly oligonucleotide to a solid support, annealing a bridging oligonucleotide to the first assembly oligonucleotide, annealing a second oligonucleotide to the bridging oligonucleotide, filling in the nick sites by ligation, and extending the nonimmobilized strand created by the bridging oligonucleotides using polymerase. *See* Hunkapiller at column 4 and Figure 1.

Applicants note in the Specification at page 2, lines 25-32 through page 3, lines 1-7 that hybridization of complementary bridging oligonucleotides has several disadvantages over the method defined by the instant claims, such as the generation of unwanted secondary structure, non-specific hybridization and the requirement to make "extra" oligonucleotides to perform the method. Hunkapiller also employs DNA ligase to perform ligations (Col. 10, lines 1-13). No other types of ligase are described for use.

Applicants invention obviates the problems associated with the strategy of Hunkapiller. The claims as amended specifically include the feature that oligonucleotides are

ligated together with ligase. Nothing in the teachings of Hunkapiller would motivate one of ordinary skill to modify the method of Hunkapiller to dispense with bridging oligonucleotides and the overlap hybridization strategy entirely. If fact, it would be contrary to the express teachings of the reference. Further, there is nothing in Hunkapiller that teaches or suggests coupling more than one oligonucleotide using a ligase to make coupled oligonucleotides prior to performing an amplification reaction to further join coupled oligonucleotides.

Finally, the statement that such strategy was one of experimental design and within the purview of the skilled artisan is merely conclusory and is not supported by a reference. Applicants respectfully request citation of a reference or an affidavit from the Examiner under 37 CFR 1.104(d)(2) if such knowledge is derived from the personal knowledge of the Examiner.

Accordingly, Applicants request withdrawal of the rejection.

B. Hunkapiller in view of Walker *et al.*

Claims 1-9, 11-15, and 17-21 are rejected under 35 U.S.C. 103(a) as obvious over Hunkapiller in view of Walker *et al.* (1975) *Proc. Natl. Acad. Sci. USA* 72(1):122-126 ("Walker").

As noted above in Section A, Applicants invention obviates the problems associated with the strategy of Hunkapiller. Nothing in the teachings of Hunkapiller would motivate one of ordinary skill to modify the method of Hunkapiller to dispense with bridging oligonucleotides and the overlap hybridization strategy entirely to join two oligonucleotides. If fact, it would be contrary to the express teachings of the reference.

The Walker reference fails to remedy the deficiencies of the Hunkapiller disclosure. Walker represents an entirely different manner in joining oligonucleotides than Hunkapiller. Further, Walker makes no mention of terminal regions of shared sequence.

Applicants earnestly submit that the claims as amended are not obvious over Hunkapiller in view of Walker and urge withdrawal of the rejection.

C. U.S. Patent No. 5,602,000 to Hyman

Claims 1-4, 6-9, 11-13, and 17-21 are rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,602,000 to Hyman ("Hyman").

Hyman discloses an enzymatic process for making oligonucleotides on a nucleotide-by-nucleotide basis. As disclosed in Hyman at Col. 10 lines 55-58, a primer is used as a substrate and a "blocked nucleotide substrate" (which is generally a nucleotide with a blocking group) is added to the 3' end. The blocking group is removed, and a second blocked nucleotide is added, and so forth until the chain is complete. The passages of Hyman cited by the Examiner do not disclose or suggest the coupling of two oligonucleotide primers to each other. Thus, the claims are not obvious over Hyman.

Accordingly, Applicants request withdrawal of the rejection.

D. Hyman in view of Langer *et al.*

Claims 1-4, 6-9, 11-13, and 16-21 are rejected under 35 U.S.C. 103(a) as obvious over Hyman in view of Langer *et al.* (1981) *Proc. Natl. Acad. Sci. USA* 78(1):6633-6637.

Hyman discloses an enzymatic process for making oligonucleotides on a nucleotide-by-nucleotide basis. As disclosed in Hyman at Col. 10 lines 55-58, a primer is used as a substrate and a "blocked nucleotide substrate" (which is generally a nucleotide with a blocking group) is added to the 3' end. The blocking group is removed, and a second blocked nucleotide is added, and so forth until the chain is complete. The passages of Hyman cited by the Examiner do not disclose coupling oligonucleotide primers to each other.

Langer is cited for disclosing biotin-labeled dideoxyuridine triphosphate. Nothing in Langer makes up for the fundamental deficiency of the Hyman reference's failure to disclose coupled oligonucleotides. Thus, the claims are not obvious over Hyman in view of Langer.

Accordingly, Applicants request withdrawal of the rejection.

Double Patenting

Claims 1-9 and 11-21 are rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-4, 7-9, 11-14 and 17-22 of U.S. Patent No. 6,635,453 to Delagrave ("Delagrave II").

Like Delagrave I, Delagrave II does not claim the feature of coupled nucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide. That feature is recognized as important when one knows that the coupled nucleotides may then be mixed and used in a PCR reaction such that longer oligonucleotides

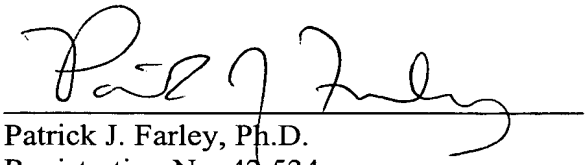
may be formed enzymatically with a variety of predictable sequences. It is the *Applicants disclosure* which teaches this, and not the claims of Delagrave I. Applicants caution against hindsight reconstruction.

Further, if the Examiner believes that the inclusion of the feature of coupled nucleotides sharing at least one terminal region of sequence with at least one other coupled oligonucleotide is merely a design choice well known in the art, Applicants request a reference supporting that assertion, or an affidavit under 37 CFR 1.104(d)(2) if such is within the personal knowledge of the Examiner.

Conclusion

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-564-8930.

Respectfully submitted,



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